

**REMARKS**

Claims 43-44, 51-52, 54-56, 60-63 and 67-69 are amended and claims 42 and 50 are canceled. Support is found, for example, in the specification as filed at page 37, line 27 to page 38, line 19 and in the original claims. No new matter is presented.

**I. Response to Claim Rejections Under 35 U.S.C. § 112**

On page 3 of the Action, claims 42, 44, 50, 52, 54-59, 61 and 63-68 are rejected under 35 U.S.C. § 112, first paragraph, on the ground that the specification does not reasonably provide enablement for treating mood disorders other than depression and major depressive disorder.

Claims 42 and 50 are canceled herein, thereby rendering the rejection moot as to these claims.

Claims 44, 52, 61 and 68 are amended herein to recite major depressive disorder or dementia with depressive symptoms.

Claims 54-56 and 63 are amended herein to recite mood disorders selected from the group consisting of depression of major depressive disorder, dementia with depressive symptoms, major depressive disorder, endogenous depression, melancholia, depression in combination with psychotic episodes, bipolar disorder with depressive phase, refractory depression, dementia of the Alzheimer's type with depressive symptoms, Parkinson's disease with depressive symptoms, senile dementia, mood disorders associated with cerebral blood vessels and mood disorders following head injury.

Applicants traverse the lack of enablement rejection and submit that the specification as filed provides sufficient guidance for one of ordinary skill in the art to practice the full scope of the claimed invention.

The fact that experimentation may be required is not dispositive since routine experimentation is permissible. Additionally, the number of working examples in the specification is only one factor to be considered. A single example can be sufficient as long as one skilled in the art would expect to be able to extrapolate that one example across the entire scope of the claims.. See MPEP § 2164.02. The question is whether the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." See MPEP § 2164.06 citing *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

In view of the above, Applicants submit that the original specification provides sufficient examples in support of the enablement of the invention. Contrary to the Examiner's position, the original specification provides more than one example employing a combination of agents within the scope of the claims.

As previously noted in the Amendment filed June 4, 2008, the original specification at pages 69 to 71 discloses a tail suspension test (Example 9), which is widely used as an experimental animal model test for predicting the antidepressant activity of a test drug in clinical settings, in which the combination of aripiprazole with citalopram is employed. The specification also provides specific examples of combinations of agents for use in the claimed methods of treatment. The activity of these agents and their usefulness in the treatment of mood

disorders as claimed is known. In view of the nature of the invention and the knowledge and skill available in the art, the description provided in the specification of the agents to be used in combination, specific combinations of the agents as claimed and the tail suspension test (Example 9), which is a well known animal model test for predicting antidepressant activity of a test drug in clinical settings, Applicants submit that sufficient guidance is provided such that the one of ordinary skill in the art would be able to practice the full scope of the claimed invention without undue experimentation.

Additionally, Example 3 at pages 51-54, discloses a forced swimming test which is also a widely used animal model test for predicting antidepressive activity of a test drug in a clinical setting. In this experimental model, a test mouse is put in a cylinder in which a suitable amount of water is contained, and the antidepressant action of a test drug is detected by measuring the immobility time, as the indication, shown by the mouse. It has been reported that the action of shortening the immobility time is correlated with clinically observed antidepressive action (Willner, P.: Psychopharmacology, 83: 1-16, 1984). The crisis of depression is closely concerned with lowering of serotonin 5-HT<sub>1A</sub> receptor neurotransmission action, and the present inventors have found that antidepressive action of antidepressants which affect the serotonin system can be detected more precisely using prolongation of the immobility time performed with WAY-100635, which is a selective serotonin 5-HT<sub>1A</sub> receptor antagonist. The prolongation of the immobility time performed by WAY-100635 is defined as the indication. In this manner, the antidepressive action of test antidepressants was determined by taking the prolongation of immobility time performed by WAY-100635 in the forced swimming test as the indication.

In Example 3 in the specification, a cylinder (diameter: 9 cm, height 20 cm), water was poured therein up to the height of 9.5 cm, from the bottom, then a mouse of ICR strain is placed

in the cylinder. After placing the mouse in the cylinder, an immobility time of 6 minutes is measured. During the test, the water temperature is maintained at 23 to 24°C. A test drug is orally administered to the mouse at 1 or 2 hours before placing the mouse in the water. WAY-100635 is administered subcutaneously to the mouse 30 minutes before placing the mouse in the water.

During this test, aripiprazole is used in combination together with citalopram, escitalopram, fluoxetine, venlafaxine or milnacipran. Following such combination administration, a decrease in the immobility time (the antidepressant activity) is observed in comparison with the case of single use of each one of aripiprazole, citalopram, escitalopram, fluoxetine, venlafaxine or milnacipran, respectively.

Further, when aripiprazole is used in combination with citalopram, escitalopram, fluoxetine, venlafaxine or milnacipran, a decrease in the immobility time (the antidepressant activity) is observed in comparison to administration of the available atypical antipsychotic drugs such as olanzapine, quetiapine, risperidone in combination with citalopram, fluoxetine, venlafaxine or milnacipran. Thus, the disclosure in the specification, taken in view of the knowledge and skill in the art and the nature of the invention provides sufficient guidance for one of ordinary skill in the art to practice the full scope of the claimed invention.

Even further, Applicants note that the comparative data provided in the Rule 132 Declaration submitted herewith also supports the enablement of the claimed invention. In this regard, Applicants note that a Declaration after the filing date of the application can be provided to demonstrate that the claimed invention works where the experiments in the Declaration employ the same steps, materials, and conditions used in the experiments in the application such that they are commensurate in scope; i.e., that the experiments used the guidance in the

specification as filed and what was well known to one of skill in the art. See MPEP § 2164.05. In the present case, the specification discloses a forced swimming test in Example 3 as described above and the data provided in the attached Declaration is also from a forced swimming test which employs the same steps materials and conditions as Example 3 in the specification. Thus, the data provided in the attached Declaration is further evidence of the enablement of the claimed invention at the time the application was filed.

Accordingly, Applicants respectfully request withdrawal of the §112, 1<sup>st</sup> paragraph, rejection.

## **II. Response to Claim Rejection under 35 U.S.C. § 102**

Claims 1, 37, 38, 40, 41, 43-45, 54, 55, 58 and 60-62 are rejected under 35 U.S.C. § 102(b) as being anticipated by Wong et al (US 2002/0156067).

Applicants traverse the rejection for the reasons of record, which are incorporated herein, and additionally based on the following.

Applicants submit that Wong et al fails to set forth any specific combinations of aripiprazole or a metabolite thereof and a norepinephrine reuptake inhibitor. Specifically, Wong et al does not show the identical subject matter, in as complete detail, as is contained in the presently rejected claims, and as is required for an anticipation under §102. In order to anticipate a claim under 35 U.S.C. § 102, a reference must disclose within the four corners of the document not only all of the elements claimed but also all of the elements arranged or combined in the same way as recited in the claim. *Net MoneyIn, Inc. v. Verisign, Inc.*, 2008 U.S. App. LEXIS 21827, 1, 27 (Fed. Cir. 2008).

For the subject matter of the presently rejected independent claims, the Examiner is relying on claims 2 and 5 of Wong et al. Claim 2 of Wong et al discloses that component (a) is

“selected from the group consisting of tandamine, pirandamine, ciclazindol, fluparoxan, lortalamine, talsupram, talopram, prindamine, nomifensine, viloxazine, tomoxetine, duloxetine, venlafaxine, milnacipran and reboxetine and mixtures thereof.” Claim 5 discloses component (b) is “selected from the group consisting of chlorpromazine, haloperidol, perphenazine, thioridazine, mesoridazine, trifluoperazine, fluphenazine, clozapine, olanzapine, risperidone, ziprasidone, quetiapine, sertindole, aripiprazole, sonopiprazole, blonanserin, iloperidone, perospirone, raclopride, zotepine, DU-127090, ORG-5222, SM-13496, amisulpride, CP-361428, Lu 35-138, balaperidone, S-18327, WAY-135452, eplivanserin, E-5842, SR-31742, NE-100, osanetant, SR-141716, SR-48692, BSF-201640, BSF-190555, LAX-101a, sarizotan, CX-691 and SB-271046 and mixtures thereof.” Thus, the possible number of combinations of one of component (a) and one of component (b) is at least in the hundreds, and most likely in the thousands. Again, one of ordinary skill in the art would be required to pick and choose among the listed compounds for component (a) and among the listed compounds for component (b) to arrive at the claimed combination of aripiprazole or a metabolite of aripiprazole and an SRI as claimed. Such picking and choosing has no place in the making of a §102 anticipation rejection. *In re Arkley, Eardley, and Long*, 172 USPQ 524, 526 (CCPA 1972).

Importantly, Wong et al does not specifically direct the reader to a composition containing a combination of aripiprazole or a metabolite of aripiprazole and an SRI as claimed, from among the hundreds or thousands of possible combinations described. Wong et al does not specifically name a composition containing a combination of aripiprazole or a metabolite of aripiprazole and an SRI as claimed. Thus, there is no reasonable basis for one to assume that one of ordinary skill in the art would specifically select a composition containing a combination of

aripiprazole or a metabolite of aripiprazole and an SRI as claimed, from among the hundreds or thousands of possible combinations described by Wong et al.

Additionally, the case law relied on by the Examiner does not specifically relate to the present situation. The claimed invention is directed to a composition comprising two different components, not a specific single compound. In order to anticipate the claim, the reference must identically disclose a composition comprising the same two components with “sufficient specificity” to constitute anticipation under 35 U.S.C. § 102. When it is necessary to select portions of teachings within a reference and combine them as in the case of Wong et al, anticipation cannot be found. More appropriately, to establish an “anticipation” rejection under §102, the reference must teach every element of Applicants’ claims. Rejections under 35 U.S.C. §102 are proper only when the claimed subject matter is identically disclosed or described in the prior art. Thus, the reference must clearly and unequivocally disclose the claimed composition without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference. As noted, such picking and choosing has no place in the making of a §102 anticipation rejection. *In re Arkley, Eardley, and Long*, 172 USPQ 524, 526 (CCPA 1972).

For at least these reasons, the present invention is not anticipated by Wong et al.

Furthermore, Wong et al fails to include any description or suggestions such that concurrent use of aripiprazole or a metabolite thereof and an SRI (serotonin reuptake inhibitor) exerts an advantageous effect on treatment or improvement for mood disorders, said effect leading to smaller dosages for treatment or improvement, so that said use can lower the side-effects and is excellently safe.

In contrast, pages 69-71 of the original specification disclose an example of an antidepressant animal model test, i.e., a tail suspension test. It can be seen that a synergistic effect was exerted when citalopram and aripiprazole were used in combination with each other, leading to a reduced dosage amount of each ingredient in said combined use. The combination therefore has excellent safety with fewer side effects. Accordingly, the present invention is not anticipated nor rendered obvious by Wong et al.

Accordingly, Applicants respectfully request withdrawal of the §102 anticipation rejection.

### **III. Response to Claim Rejection under 35 U.S.C. § 103**

Claims 38, 39, 46-53, 56-57 and 63-69 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Wong in view of Winnans (American Journal of Health-System and Pharmacy, Vol. 60, Dec. 1, 2003; pages 2437-2447).

The Examiner admits that Wong et al does not specifically teach metabolites of aripiprazole or dehydroaripiprazole, etc., or wherein aripiprazole is anhydrous aripiprazole crystals B or the norepinephrine reuptake inhibitor to be specifically escitalopram or citalopram.

The Examiner relies on Winans as teaching that the major metabolite of aripiprazole is dehydro-aripiprazole which has demonstrated similar affinities for D<sub>2</sub> receptors and represents approximately 40% of aripiprazoles' AUC in the plasma. Additionally, the Examiner states that Winans teaches that when aripiprazole was administered with divalproex, a moderate change in pharmacokinetic parameters was observed and similar effects were observed when the active metabolite was administered with divalproex. Thus, the Examiner considers that the substitution

of aripiprazole taught by Wong with its metabolites such as dehydro-aripiprazole would have been *prima facie* obviousness.

Regarding the specific SRI's citalopram and escitalopram, the Examiner states that these two drugs elicit anti-depressant effects by inhibiting serotonin reuptake and although Wong et al is silent as to these specific drugs, Wong et al mentions venlafaxine, which also inhibits serotonin reuptake as evidenced by Harvey et al and Owens. Thus, the Examiner considers that venlafaxine is a functional equivalent of citalopram and escitalopram, and thus the substitution of the antidepressants taught by Wong with other similarly functioning drugs such as citalopram or escitalopram would have been obvious.

Applicants traverse the rejection and submit that the Examiner has not made a *prima facie* showing of obviousness based on the following.

In determining the difference between the claimed invention and the prior art, the proper inquiry is whether the invention as a whole would have been obvious and not whether the differences themselves would have been obvious.

In the present case, the claimed invention is directed to a composition comprising aripiprazole in combination with a specific SRI such as escitalopram or citalopram. The Examiner has not properly identified a teaching or suggestion in the prior art which may have served as motivation for one of ordinary skill in the art to combine the cited references with a reasonable expectation of achieving the claimed invention as a whole. Instead the Examiner has compared individual elements in the claims to the prior art, and asserts obviousness of the elements as opposed to the claimed invention as a whole.

That is, there is no apparent reason for one of ordinary skill in the art to combine the references as suggested with a reasonable expectation of success in achieving the claimed invention. Specifically, Wong et al teaches venlafaxine as a norepinephrine reuptake inhibitor and specifically mentions venlafaxine as an example, but does not mention escitalopram or citalopram. Harvey et al teaches that venlafaxine has dual mechanisms of action, i.e., serotonin and norepinephrine uptake inhibition over its clinically relevant dosage range. On the other hand, citalopram and escitalopram are described as potent selective SRI's. Considering that Wong et al teaches a composition comprising a norepinephrine reuptake inhibitor, one of ordinary skill in the art would not have been motivated to substitute the potent SRI's citalopram or escitalopram and to further combine the potent SRI's with aripiprazole or its derivatives as claimed based on the teachings of the references, since citalopram and escitalopram are not disclosed as having a dual mechanism of action or norepinephrine reuptake inhibition activity.

Further, with respect to the Examiner's assertion that venlafaxine is a functional equivalent of citalopram or escitalopram, Applicants submit that in order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art. The mere fact that the components at issue may be functional equivalents alone is not sufficient. See MPEP §2144.06. In this case, venlafaxine has dual functions as a serotonin reuptake inhibitor and as a norepinephrine uptake inhibitor, whereas escitalopram and citalopram are selective serotonin reuptake inhibitors. Therefore, escitalopram and citalopram would not be considered as functional equivalents to venlafaxine by those of ordinary skill in the art as asserted by the Examiner.

In view of the above, one of ordinary skill in the art would not have been motivated to combine the references with a reasonable expectation of success. For at least this reason the present invention is not rendered obvious by the cited references, whether taken alone or in combination.

Moreover, the present invention provides unexpectedly superior results as shown by the comparative test data provided in the attached Declaration under 37 C.F.R. §1.132. In the Declaration, dehydroaripiprazole and escitalopram are selected as the metabolite of aripiprazole and the SRI, respectively. Escitalopram is one of the enantiomers (S-enantiomeric form) of the racemic body scitalopram and was known to have a similar pharmacological effect as escitalopram at the filing date of the present application.

As the combined agents to be compared, those disclosed in Examples 1 and 2 of Wong et al, i.e., a combination of a neuroleptic (risperidone, olanzapine, clozapine) and an NRI (reboxetine) are selected. A forced swimming test was employed using mice, which is an animal model devised for evaluating anti-depressive effects of an agent. The purpose of the test is to compare the effects of the combination of aripiprazole and six SRI's (duloxetine, venlafaxine, milnacipran, escitalopram, paroxetine, sertraline) and dehydroaripiprazole and SRI (escitalopram) versus the combination of the three antipsychotic agents (risperidone, olanzapine, clozapine) and the NRI (reboxetine) on the immobility time. The results shown in Tables 1-3 of the Declaration establish that the combination of the present invention (aripiprazole and duloxetine, venlafaxine milnacipran, escitalopram, paroxetine or sertraline, and dehydroaripiprazole and escitalopram) clearly shorten the prolonged immobility time in the forced swimming test of mice, which means that the combination of the present invention has antidepressive effects. On the other hand, the combinations described in Wong et al

(risperidone, olanzapine or clozapine and reboxetine) did not significantly shorten the prolonged immobility time in the forced swimming test of mice. Therefore, the combinations of the present invention, which are not specifically disclosed by Wong et al (i.e., the combination of aripiprazole and duloxetine, venlafaxine, milnacipran, escitalopram, paroxetine or sertraline, and dehydroaripiprazole and escitalopram) have synergistic effects which are completely unexpected from the references.

In summary, Wong et al does not disclose nor suggest the inventive combination or the advantageous effects of the present invention at all. The Winnans reference does not remedy the deficiencies of Wong et al. Therefore, the present invention is patentable over the cited art for these additional reasons.

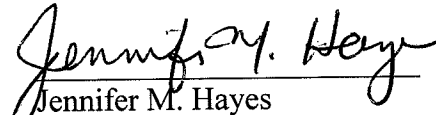
Accordingly, Applicants respectfully request withdrawal of the §103 obviousness rejection.

#### **IV. Conclusion**

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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